Remarks

Claims 1, 4-13 and 15-27 are pending. Claims 5-14, 17 and 18 have been cancelled. The Applicants reserve the right to file one or more divisional applications. Claims 4 and 24 have been amended. Claims 28 to 30 are new claims. The specification is amended as described above. Support for the amendments and new claims may be found at, for example, at page 23, lines 14 to 21, page 25, lines 7 to 10 and lines 15 to 18, page 27, lines 16 to 19, page 37, lines 10 to 12, page 47, line 17 and page 61, line 19 of the originally filed application. Certain of the amendments are also merely made for the sake of clarity. The Applicants respectfully request entry of the amendments and new claims which are believed to place the application in better condition for allowance or, alternatively, appeal. Claims 1,4, 15-16 and 19-27 are rejected.

In response to the Notice to Comply, the Applicants provide a copy of a sequence listing as well as a copy of the sequence listing in computer readable form. The Applicants also provide a statement that the content of the copy of the sequence listing and the computer readable form of the sequence listing are the same and include no new matter. Entry of the sequence listing into the specification has also been respectfully requested.

The specification is also objected to under 37 CFR §1.821 as not containing appropriate sequence identifiers for the amino acid sequence TAEKLK (SEQ ID NO: 1). However, the Applicants respectfully note the amino acid sequence TAEKLK is identified as SEQ ID NO: 1, in all instances where it occurs, in both the specification and claims. Moreover, the figures in the application do not appear to contain amino acid sequences or nucleic acid sequences.

The Applicants respectfully request withdrawal of the objections to the specification.

Claim 24 has been objected to as an improper dependent claim under 37 CFR §1.75(c). Claim 24 has been amended such that it no longer recites "may" and now further limits the subject matter of Claim 1. Thus, Claim 24 is now a proper dependent claim.

The Applicants respectfully request withdrawal of the objections to Claim 24.

Claims 1, 4, 15-16 and 19-27 are rejected under 35 USC §112, first paragraph, as failing to satisfy the written description requirement.

Claims 1, 4, 15-16 and 19-27 satisfy the written description requirement. Reasons are set forth below.

The Applicants submit that the present application provides an adequate written description of the recited compounds as it provides a precise definition and description of the compounds of the claims. This definition and description provides relevant, identifying characteristics of the compounds in the form of functional characteristics coupled with the disclosure of a correlation between function and structure.

The functional characteristics of the compound is the modulation of the function of beta 1 integrin by the compound resulting in at least one of (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix. The present application provides a screening method to identify compounds which possess these functional characteristics.

There is also a correlation between function and structure. In particular, the application discloses a relationship between the desired functional characteristics and a structure which binds to the beta 1 integrin molecule in the region of amino acid residues 82 to 87 comprising residues TAEKLIK (SEQ ID NO: 1) of the sequence of the mature beta 1 integrin molecule.

The Official Action asserts there is no described or art-recognized correlation or relationship between the structure of recited compounds and their beta 1 integrin modulation function. However, the Applicants submit that this is in error as there is, in fact, a relationship between the structure of the recited compounds and their beta 1 integrin modulation function--the relationship being that the compound must bind the region of amino acid residues 82 to 87 of the sequence of the mature beta 1 integrin molecule comprising residues TAEKLK (SEQ ID NO: 1) in order to have the desired beta 1 integrin modulation function.

As noted in the present application at page 11, line 26 to page 12, line 3, each domain of beta 1 integrin appears to possess a different function. Hence, binding to different domains may entail different downstream intracellular signaling resulting in different functional outcomes. The present Application identifies the specific domain to which the compound for use in the present invention must bind, and thus describes a relationship between the structure of the recited compounds and their beta 1 integrin modulation function. The Applicants therefore submit that one of ordinary skill in the art could therefore instantly envisage, based on the present disclosure, a genus of compounds each of which bind the identified region of beta 1 integrin and retain the essential functional features.

The Applicants therefore submit the application provides a precise definition of the recited compounds, that the definition provided comprises functional characteristics coupled with the disclosure of a correlation between function and structure, and that this is sufficient to show the Applicants were in possession of the recited genus of compounds identified in the claims. The Applicants therefore submit the application provides an adequate written description and that the recited compounds are described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that they, at the time the application was filed, had possession of the subject matter of the claims.

The Applicants further submit the definition of the recited compounds differs from the definition of the compounds in the case of Univ. of Rochester v. G.D. Searle & Co. in that the recited compounds are defined as binding to a specific site and this binding correlates to the desired functional activity of the compounds. In contrast, the definition provided in the case of Univ. of Rochester v. G.D. Searle & Co. appears to have been solely in terms of functional activity.

The Applicants respectfully request withdrawal of the written description rejections.

Claims 1, 4, 15-16 and 19-27 are rejected under 35 USC §112, first paragraph, as non-enabled.

Claims 1, 4, 15-16 and 19-27 are enabled. Reasons are set forth below.

The Applicants submit that the present application describes structural and functional characteristics of the compounds of the claims. The structural features are the sequence of the beta 1 integrin molecule to which the recited compounds bind. The functional characteristics are the ability to modulate beta 1 integrin activity and produce at least one of (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix. Furthermore, the Applicants respectfully submit one of ordinary skill in the art would have no difficulty in obtaining compounds which bind to the identified region of the beta 1 integrin molecule and modulate its function as described. Such compounds, for example, may include other antibodies in addition to the JB1a antibody. As indicated in the description of the present application at page 31, lines 16 to 21, antibodies for use in compositions and methods of the claims can be readily prepared without undue experimentation. This is routine, where the epitope is known (as it is here), and such antibodies can be easily prepared by one of ordinary skill in the art according to standard techniques and procedures for immunizing animals, such as mice, with protein

epitopes and the selection of hybridomas that produce immunogen specific monoclonal antibodies. The Applicants further submit that the recited compounds are not restricted to antibodies, but may also include, for example, synthetic peptides. Thus, the Applicants also submit that one of ordinary skill in the art would automatically know how to make such a peptide which binds the identified region of the beta 1 integrin molecule without undue experimentation using well known techniques. A person of ordinary skill in the art could then, without undue experimentation, use the screening methods disclosed in the application to select from the antibodies/peptides which bind the identified region of beta 1 integrin and those which have the desired modulatory effect on the function of beta 1 integrin. The Applicants therefore submit that the present application teaches one of ordinary skill in the art how to make and use the recited compounds without undue experimentation. Stated differently, the Applicants respectfully submit the full scope of the claims is enabled.

The Applicants also note page 11, line 17 to page 12, line 13 of the description of the application explains that integrins have several functions. The Applicants submit the same compound may serve to inhibit one function of beta 1 integrin and to stimulate another function. This is supported by the attached Declaration under 37 CFR §1.132 by Dr. Rehab Al-Jamal, one of the inventors of the claimed subject matter. This Declaration includes experimental data (Appendix B) supporting the role of the anti-beta 1 antibody, JB1a, as both an agonist and an antagonist which is demonstrated by its effect on downstream signaling with and without injury and its conformation effect from the FRET. As noted on page 12, lines 8 to 13 of the present application, the use of the functional modification terminology serves best to take this dual function as an agonist and an antagonist of beta 1 integrin into account. The Applicants further submit the claims do not encompass compounds which both inhibit and enhance apoptosis as only compounds which inhibit apoptosis are disclosed, and that the claims refer to compounds which alter the MMP balance, rather than compounds which both inhibit and enhance MMP balance.

The Applicants also wish to make several comments regarding the teachings of Grose. For instance, on one hand Grose appears to teach keratinocytes are not totally dependent on beta 1 integrin to heal wounds, that other integrins appear to compensate at least partially for the lack of beta 1 integrin, that the keratinocyte proliferation rate in beta 1 null keratinocytes is not reduced in early wounds and that the keratinocyte proliferation rate in beta 1 null keratinocytes is increased in late wounds. However, Grose also states that:

> Ultimately, beta1-deficient epidermis did cover the wound bed, but the epithelial architecture was abnormal. These findings demonstrate a crucial role of beta 1 integrins in keratinocyte migration and wound re-epitelialisation.

See Grose at 2303 (emphasis added). Grose, therefore, clearly teaches that beta 1 integrin has an important ("crucial") role in tissue repair although this role may be partially compensated for in the absence of beta 1 integrin.

The Applicants also wish to make several comments regarding the teachings of Zweers. For instance, on one hand Zweers appears to teach that alpha 2 beta 1 is dispensable for reepithelialisation. However, Zweers also teaches that wound tensile strength was reduced in alpha 2 beta 1-null mice which indicates the tissue was less deformable and suggests subtle changes in the organization of the extracellular matrix. *See* Zweers at 474. This means Zweers supports a role for beta 1 integrin in tissue repair. Zweers also states that "[i]n this study, we demonstrate that alpha 2 beta 1 integrin has important, but unexpected, roles in murine cutaneous tissue" *See* Zweers at 473. It is also noted that Zweers teaches that alpha 2 beta 1 is dispensable for reepithelialisation, but does not teach that all beta 1 integrin receptor types are dispensable for reepithelialisation.

In summary, neither Grose nor Zweers suggests the methodology exemplified in the present specification could not be extrapolated to other disease conditions. Instead, these documents support an important role for beta 1 integrin in tissue repair.

Importantly, the Applicants respectfully submit demonstrating that an *in vivo* treatment regiment with anti-beta 1 antibodies promotes tissue repair. This is apparent from the attached Declaration by Dr. Rehab Al-Jamal. In particular, the Declaration provides data demonstrating the anti-beta 1 antibody, JB1a, is effective in the treatment of Parkinson's disease (*in vivo* data), arthritis (*in vivo* and *in vitro* data) and Alzheimer's (*in vitro* data) in art accepted models. The results of *in vivo* testing with JB1a in a mouse model of Parkinson's disease are attached to the Declaration as Appendix A. This testing showed that *in vivo* treatment with the anti-beta 1 antibody JB1a promoted tissue repair in a mouse model of Parkinson's disease (Figs. 5 and 9).

The Official Action also asserts the art teaches alpha 2 beta 1 is dispensable for reepithelialisation and teaches tissue repair in beta 1 integrin deficient animals. The Applicants submit that, as discussed above, even if limited tissue repair is possible in the absence of beta 1

integrin, this does not mean that beta 1 integrin has no role in tissue repair. The Applicants further submit that the overall teachings of Grose and Zweer, as discussed above, support a role for beta 1 integrin in tissue repair.

In view of the above discussion, the Applicants submit that one of ordinary skill in the art can readily make, and use, the claimed subject matter without undue experimentation.

The Applicants respectfully request withdrawal of the enablement rejections.

Claims 1, 4, 15-16 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark and Binda. Reasons are set forth below.

Clark fails to teach all the elements of the claims. Clark does not teach the use of the compounds recited in the claims because Clark only teaches the use of polyclonal antibodies to fibronectin and fibronectin (alpha 5 beta 1) receptor. Clark is also silent concerning the clone used to produce these antibodies or the epitope to which the antibody binds. As noted in the application, the functional modification of beta 1 integrin observed in the presence of an antibody which binds beta 1 integrin is epitope dependent. In fact, binding to the region of amino acid residues 82 to 87 comprising residues TAEKLK (SEQ ID NO: 1) of the sequence of the mature beta 1 integrin molecule has been observed to result in functional modulation of beta 1 integrin leading to at least one of (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix, as claimed in the present invention. Clark does not teach the use of an antibody which binds to this region. The recited limitations involving alteration in MMP balance, inhibition of the apoptosis pathway and increase in anabolism of the ECM also cannot be considered inherent properties of the antibodies in Clark. Moreover, it is axiomatic to say that which is inherent cannot be obvious. *See e.g.*, In re Spormann and Hienke, 150 USPQ 449 (CCPA 1996).

The Applicants also submit there is no teaching in Clark that the compounds taught therein inhibit the fibronectin receptor from binding its ligand fibronectin. Clark studied fibronectin matrix deposition and fibronectin receptor expression in healing and normal skin. The model of skin wound healing used in Clark exemplifies a successful physiological repair in the absence of intervention. This is unlike disease conditions such as emphysema, arthritis and neurodegeneration where repair or wound healing does not occur, but rather tissue scarring or abnormal remodelling is a key feature. Antibodies to the fibronectin receptor were used to map the expression of the fibronectin receptor

and to determine if fibronectin receptor expression occurred co-ordinately with fibronectin deposition in areas of cell migration. *See* Clark at 103S, Figs. 1 and 3.

There is no teaching in Clark of the use of antibodies that inhibit the fibronectin receptor from binding its ligand fibronectin. On the contrary, in Clark, fibronectin and fibronectin receptors were observed to occur in concert during epidermal migration over a wounded surface. This led Clark to suggest that fibronectin and fibronectin receptors may facilitate this migration. *See* Clark at 133S. Therefore, it is assumed on the basis of this work that the fibronectin receptor, alpha5beta1 integrin, is increased during the wound repair process. This means one of ordinary skill in the art, based on the disclosure in Clark, would therefore conclude that inhibition of beta 1 integrin would be detrimental in promoting tissue repair. Stated differently, one of ordinary skill in the art would not be motivated to modify Clark, or combine it with Binda, as suggested in the Official Action or expect success on so doing.

In Binda, the JB1a antibody is classified solely as an inhibitory antibody. The dual functional effect (agonist/antagonist) of the JB1a antibody on both signaling and conformation of beta1 integrin is not disclosed by Binda, nor was this dual functional effect known at that time as this effect was only identified at a later stage by subsequent work carried out by the Applicants.

Altogether, this means a person of ordinary skill in the art would have concluded from the disclosure in Binda and Clark that inhibition of beta 1 integrin would be detrimental in promoting tissue repair. Such a person of ordinary skill in the art would consequently not have been motivated to use the JB1a antibody in promoting tissue repair, because this antibody was considered to be an inhibitory antibody. This also means Binda fails to correct the deficiencies of Clark.

It is further noted that, in the claims, beta1 integrin is targeted irrespective of the alpha partnering chain. While the work of Clark suggests that the fibronectin receptor is important for successful wound healing, it does not discuss the interplay of the various beta 1 integrin-containing heterodimers during the process of wound healing. *See* Clark at 130S.

In view of the above discussion, the Applicants submit that Clark and Binda fail to teach all the elements of the claims and that one of ordinary skill in the art would not be motivated to modify Clark, or combine it with Binda, as suggested in the Official Action or expect success on so doing. Stated differently, the Applicants submit that the rejection fails to establish *prima facie* obviousness.

The Applicants respectfully request withdrawal of the obvious rejections made over Clark and Binda.

Claims 1, 4, 15-16 and 20-27 are rejected under 35 USC §103(a) as being unpatentable over Hérard and Binda. Reasons are set forth below.

Hérard fails to teach all the elements of the claims. Hérard does not teach the use of the compounds recited in the claims because Hérard only teaches the use of anti-integrin (P5D2 targeting the amino acids 207-218 and known to be inhibitory) or anti-fibronectin antibodies. As noted in the application, the functional modification of beta 1 integrin observed in the presence of an antibody which binds beta 1 integrin is epitope dependent. Binding to the region of amino acid residues 82 to 87 comprising residues TAEKLK (SEQ ID NO: 1) of the sequence of the mature beta 1 integrin molecule has been observed to result in functional modulation of beta 1 integrin leading to at least one of (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix, as recited in the claims. Hérard teaches only the use of an antibody which binds to a different region, but does not teach the alteration in MMP balance, inhibition of the apoptosis pathway and increase in anabolism of the ECM. Moreover, the recited limitations involving alteration in MMP balance, inhibition of the apoptosis pathway and increase in anabolism of the ECM cannot be considered inherent properties of the antibodies in Hérard. Moreover, it is axiomatic to say that which is inherent cannot be obvious. *See e.g.*, In re Spormann and Hienke, 150 USPQ 449 (CCPA 1996).

The Applicants also submit that the Official Action appears to have overlooked that Hérard teaches using anti-integrin or anti-fibronectin antibodies in wound-repair **blocking** experiments. In these experiments the use of these antibodies resulted in a significant decrease in the wound-repair index in the presence of either anti-beta 1 or anti-fibronectin antibodies, while the addition of fibronectin to the culture medium induced a significant increase in the wound repair index. These results suggest that fibronectin and the corresponding alpha 5 beta 1 integrin play an important role in the process of airway epithelium wound repair. Hérard also discloses that the alpha 5 beta 1 integrin receptor has been reported to play an essential role in the assembly of the fibronectin matrix. *See* Hérard at L732. Therefore, Hérard clearly teaches that inhibition of beta 1 integrin inhibits wound repair--a conclusion which was also implied by Clark.

In Binda, the JB1a anbibody is classified solely as an inhibitory antibody. The dual functional effect (agonist/antagonist) of the JB1a antibody on both signaling and conformation of beta1 integrin is not disclosed by Binda. This dual functional effect also was not known at that time and was only identified at a later stage by subsequent work carried out by the Applicants. Hérard teaches that inhibition of beta 1 integrin is detrimental in promoting tissue repair. This means that Hérard teaches away from the use of the JB1a antibody, which was at the time considered an inhibitory antibody, in promoting tissue repair. Moreover, Binda fails to correct the deficiences of Hérard.

In view of the above discussion, the Applicants submit that Hérard and Binda fail to teach all the elements of the claims and that one of ordinary skill in the art would not be motivated to modify Hérard, or combine it with Binda, as suggested in the Official Action or expect success on so doing. Stated differently, the Applicants submit that the rejection fails to establish *prima facie* obviousness.

The Applicants respectfully request withdrawal of the obvious rejections made over Clark and Binda.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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